REMARKS

Comments on Applicant's Inventions

Applicant does not claim to have broadly invented a combination of sodium phosphate (herein "NaP") and polyethylene glycol (PEG) for use as a bowel lavage - the known use of each of these materials alone for bowel lavage is discussed, *inter alia* in Applicant's specification. The compositions Applicant has invented and claims are specific compositions comprising NaP and PEG in certain amounts and proportions Applicant has found necessary to provide both adequate cleansing of the bowel for, e.g., colonoscopies, and a product well-tolerated by patients which leads to higher patient compliance and consequently improved bowel cleansing.

As set forth at length in Applicant's response of 5 April, 2005, particularly pages 15-17 and Exhibits A, B and C thereof, Applicant has demonstrated that, in comparison to commercial PEG lavages such as GoLytely® and sodium phosphate purgatives such as Fleet Phospho-soda®, the present claimed compositions reduce or eliminate the prevalent unpleasant side effects such as nausea, vomiting, abdominal cramps, symptoms of electrolyte imbalance, and poor taste associated with these NaP purgatives; and the bloating and attendant nausea and poor associated with these high-volume, high-PEG concentration lavages. Thus, patient compliance is high. They also permit the use of the simplified methods of administration reflected in Applicant's method claims.

The physical properties of the claimed "dry prep" compositions, which contain admixtures of dry, water-soluble NaP and PEG, permit the dosages to be readily constituted by the patient with an amount of aqueous liquid within the control and to the liking of the patient. Usually a quart or less liquid, as compared to, e.g., the four liter dosage required by GoLytely® lavages, is needed, due in part to the smaller proportion of PEG in the present compositions. Further, typically only one or, more usually, two doses are required to achieve bowel evacuation,

rather than the multiple doses of commercial PEG products, or the two-day cleanouts typically required by commercial NaP products. Further, the conservative make-up of the compositions permit the formulation of the compositions without the electrolytes which are added to commercial PEG lavages such as GoLytely to restore electrolyte balance disrupted by the large volumes of liquid used in these products. This significantly improves the taste of Applicant's compositions. Additionally, these physical properties facilitate packaging and shipping of the product, with concomitant savings.

These issues were discussed at length in Applicant's 4 April 2005 response to the rejection of the claims under 35 USC 103(a) for obviousness over WO 98/43654 (PCT), in view of Cleveland *et al.*, U.S. 6,048,901; Wood *et al.* U.S. 5,498,425; and Vining, U.S. 5,782,762, in the Office Action of 15 July 2005. In a telephone interview with Applicant's attorney following the 4 April 2005 response, the Examiner indicated that the claims were in condition for allowance. In a subsequent interview, the Examiner indicated he was re-opening prosecution, after uncovering new prior art; this was followed up with the present outstanding Office Action.

Accordingly, Applicant relies herein on the remarks and evidence of record addressed to the issues raised by the Examiner as to the PCT, Wood *et al.*, Cleveland *et al.* and Vining art previously applied, and addresses only the new art cited by the Examiner: Matsuoka *et al.*, Sobrino-Faya *et al.*, and the PDR (*infra*) and their combination with the earlier-addressed art, as applied in the substantive rejections herein.

The Rejections

The Examiner rejects Claims 1-41 under 35 USC §103(a) as unpatentable over WO 98/43653 (PCT) in view of Wood *et al.*, U.S. 5,498,425 and Vining, U.S. 5,782,762, in further view of Kaoru Matsuoka *et al.*, Therap. Res. 17:189-192, 1996 (herein

referred to as "Matsuoka"); and the Physician's Desk Reference (PDR), 49th ed. 1995.

The Matsuoka reference, entitled "The Evaluation of Using Oral Sodium Phosphate, referred to [sic] FLEET, and PEG Prior to Preparation for Colonoscopy", was applied as an English language Abstract of a Japanese publication; an English language translation of the whole publication is submitted herewith (Exhibit E), accompanied by the c.v. of the translator.

Matsuoka describes an evaluation of "commonly used" Fleet, presumably Fleet Phospho-soda®, for use as a bowel evacuant, in combination with 1000 ml PEG prior to colonoscopy. The "constituent of Fleet" is clearly described in Table 1 as consisting of 48g diphosphate plus 18g monophosphate per 100 ml water. However, the PEG constituent is not further described.

In the Preface to this study, it is stated that, "... the patient received 90 ml Fleet with an equal volume of water mixed with 1000 ml of PEG once on the morning of the day of preparation for the colonoscopy. The side effects were observed including the oral lavage, the subject's symptoms due to the large dosage taken and the clinical research testing.". According to this description, the dosage of sodium phosphate (NaP) was 59.4g of NaP (90% of the 66g present in the 100 ml solution of Table 1). This is well outside Applicant's broadest claimed single dosage range of 5-45g NaP.

The Examiner cites the PDR - without explicitly asserting its presumed application (if any) to Matsuoka - as describing dosages for Fleet Phospho®-soda as 45 ml (1.5 fluid oz), containing per teaspoonful (5 ml) 2.4g Na monophosphate and 0.9 g Na diphosphate). What is not mentioned in the PDR is that the "commonly used dosage", at least in the U.S., is twice that - one 45 ml dose the evening before the colonoscopy and one the day of the procedure, for a total NaP dosage of 59.4 g in 90 ml of solution, consistent with the definition of the amount of Fleet constituent used in the"Preface" of the Matsuoka article in a single dosage (see "Fleet Phospho-soda® Bowel Preparation

Instructions", submitted herewith as Exhibit F). Again, this is well above the amount of NaP of Applicant's claimed single dosages in claims 13-15 and 28-30 of 5-45g phosphate powder, which may at least partially account for the "nausea due to the salty taste" experience by 21.1% of the patients in the study (p. 4). It also may be due to the fact that the administration of NaP preceded that of the PEG by up to one hour in Matsuoka's study.

The Examiner further points to the description of GoLytely® in the PDR "PEG 3350 and electrolytes for oral solution contain[ing] 236 g of PEG which is in powder form to be reconstituted with four liters of water.", but again does not relate this disclosure to his primary references.

Matsuoka refers only to "oral PEG"; it is not further described with respect to PEG content, nor is it referred to as 1000 ml of a "standard" PEG solution.

However, the Examiner appears to be suggesting here that "GoLytely®" can be read into the Matsuoka publication to supply the missing essential information for formulating PEG. This publication was written by self-proclaimed researchers, who may well have concocted their own (and unknowable) PEG solution. Further, the Examiner fails to mention another commercial product described in the PDR, NuLytely®, which adds four liters of water to nearly twice as much PEG and electrolytes as GoLytely®, 420g (PDR pg. 658). Also, Japan may well have different versions of such products. "Oral PEG" might be the equivalent of any or none of these; the composition of "oral PEG" here is pure speculation. Further, the publication suggests that the 1000 ml PEG used is a decreased dosage of the "2000 ml oral PEG... familiar in the preparation for colonoscopy"; i.e., half the standard dose of this unknown product. Both GoLytely® and NuLytely® require four liters of water with a half-dosage requiring two liters.

In sum, the teachings of this publication would not enable one skilled in the art to even reproduce the authors' materials or methods, let alone arrive at Applicant's claimed

compositions and methods for bowel cleansing. The Examiner's grounds for rejection are based on hindsight, and reading into the publication essential facts without basis. Accordingly, it is submitted that Applicant's inventions are not *prima facie* obvious over either Matsuoka alone or in combination with the PDR, or in further combination with the PCT, Wood *et al.*, or Vining, and reconsideration and withdrawal of this ground of rejection is earnestly solicited.

Further, in rebuttal of any presumption of *prima facie* obviousness, Applicant refers the Examiner to the observed side effects which were an object of the Matsuoka study. 21% of the 38 patients experienced nausea, and nearly eight percent experienced stomach pain and/or abdominal cramp or fullness (Table 2). Also, nearly eight percent (7.8%) of the patients complained of discomfort, dizziness and rash (Table 2), and an unknown number objected to the "salty taste" (pg 4, ¶3). In all, nearly a third of the patients (31.6%) had adverse side effects, of the type which were rare or absent in Applicant's results. [Note: the authors state in their "Results" section that none of the patients complained of discomfort - this is contradicted in their data shown in Table 2.] In contrast, Applicant's patients (he is a gastroenterologist) had virtually no complaints (see record). Accordingly, reconsideration and withdrawal of this ground of rejection is accordingly requested.

The Examiner's combination of the PDR and Matsuoka references with the PCT document, Wood *et al.*, and Vining is not clearly understood. As previously discussed at length in the earlier prosecution, the PCT document merely provides an extensive list of possible combinations of what is probably the large part of every known laxative or purgative. The Examiner appears to suggest that, in view of Matsuoka and the PDR, it would be obvious to select and combine the PEG and NaP laxatives/lavages disclosed in the PCT to provide Applicant's bowel cleansing composition. However, since Matsuoka broadly describes an NaP/PEG lavage compositions, and the PCT adds

nothing to the deficient Matsuoka disclosure in terms of teaching the making and using of Applicant's composition as claimed, the rationale for the combination of references as applied by the Examiner is not clear.

The teachings of Wood *et al.* and Vining, as previously stated, relate to the known uses of cascara and bisacodyl, and clear liquid diets with prior art bowel lavages. Applicant does not contend that these adjuncts are per se novel and unobvious, only that their use in combination with the present lavage compositions and methods is.

The Examiner further has rejected Claims 1-43 under 35 USC 103(a) over the PCT, in view of Wood *et al.*, Vining, and Cleveland *et al.*, U.S. 6,048,901 in further view of the PDR and Sobrino-Faya *et al.*, Supplement to Gastroenterology 122:A-334, April 2002 (Abstract).

However: Sobrino-Faya *et al.* describe compared bowel lavages for hospital patients, one of which comprises the use of "90 ml NaP and 1500 ml PEG", comprising an "addition of half dose PEG to a standard dose of NaP without affecting tolerance." As noted above, Fleet Phospho-soda® is used in dosages of 90 ml, and it may be reasonable to consider that this formulation was "standard" solution used as the NaP constituent. Again, however, the publication is silent on the strength of the PEG solution. Again, the Examiner turns to the PDR to make up this deficiency, but there is no justification for the apparent assertion that the PEG product used was GoLytely®. In fact, it clearly was not - a one-half dose of GoLytely® (see PDR) is 2 liters - while Sobrino-Faya's half-dose is 1500 ml (1.5 liters).

As initially discussed, Applicant's claims define specific compositions and methods for using them. It is the specified proportions and amounts of PEG and NaP for administration, and the methods for using them which provide the demonstrated results. None of the references cited in this application suggest these limitations. Composition claims 1-12 require specific proportions of NaP to PEG; these are not

suggested by Sobrino-Faya, as there is no enabling disclosure as to the make-up of the PEG described in this article. With respect to the single dosage compositions, assuming arguendo that an equivalent of the Fleet Phospho-soda® reported in the PDR was used, the single PEG/NaP dosage used by Sobrino-Faya contained 59.4g in the 90 ml used. This amount is far above the broadest NaP range recited in the composition single dosage claims: 5-45g sodium phosphate powder.

Additionally, with respect to both these claims and the method claims, Sobrino-Faya does not reveal whether his PEG was mixed with NaP, or taken separately. Further, Sobrina-Faya discloses liquid constituents, while Applicant provides dry PEG and NaP compositions, which are easy to dissolve and administer, and which give the patient some control over the volume of liquid which he or she chooses to dissolve them in, as discussed at more length *supra*.

Again, the combination of the secondary references with the primary references PCT, Wood *et al.*, and Vining is not clear, for the same reasons as set forth above. Cleveland *et al.* uses his PEG non-electrolyte solution to inhibit symptoms of constipation. In contrast, Applicant has developed a PEG-based lavage which does not require electrolytes to re-balance the system, as do the PEG lavages of the prior art. The teachings of Cleveland are remote.

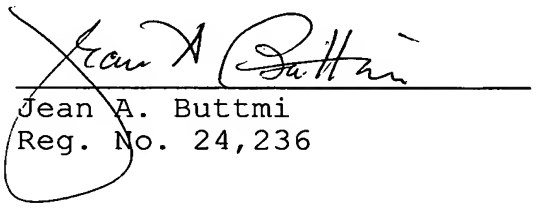
Accordingly, it is submitted that claims 1-43 are not *prima facie* obvious over WO 98/43653, in view of Wood *et al.*, Vining, and Cleveland *et al.*, in further view of Sobrino-Faya and PDR, reconsideration and withdrawal of this rejection is earnestly solicited.

The Examiner has further rejected claims 40, 42, and 43 under 35 USC §112, 2nd paragraph as indefinite with respect to the wording thereof. Claims 42 and 43 have been amended to reflect that the supplemental electrolytes referred to are other than those in the claimed PEG/sodium phosphate compositions; e.g., these claims exclude PEG bowel lavages such as GoLytely and

NuLytely which contain PEG and electrolytes needed to counteract electrolyte loss owing to the large volume of PEG solution to be ingested. Antecedent basis is found on page 2, paragraph 3, lines 9ff. Claim 40 has been rewritten to state that the sodium phosphate is added to the PEG as a powder.

In view of the foregoing remarks and cited evidence, reconsideration and withdrawal of the present rejection of claims 1-43 under 35 USC 103(a) for obviousness is respectfully requested and an early notice of allowability of these claims and the newly added dependent claims is earnestly solicited.

Respectfully submitted,



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Resume

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Objective: To work as as a Japanese Instructor

Summary of Qualifications

Work Experiences

Current -	Substitute teacher for El Paso Independent School Districts Teacher at El Paso Japanese Supplementary School (Saturdays)
1999-2003	Faculty at Hacienda Heights Communications Magnet School, Ysleta Independent School District
1998-1999	Japanese Teacher at Burges High School
1997-1998	Substitute Teacher for El Paso Independent School District
1980-1993	Teacher's Aide (Country Day School, Preschool, etc.)

In Japan

1969-1970	Squibb Japan, Tokyo; Executive Secretary
1968-1969	Anderson, Mori and Rabinovitz Law Firm, Tokyo; Executive Secretary
1963-1968	Research Laboratories, Sankyo Co., Ltd.; Executive Secretary
1958-1963	Kwassui Junior College, English Department, Nagasaki; Assistant

Education

1992-1997	The University of Texas at El Paso - Bachelor of Interdisciplinary Studies
1956-1958	Kwassui Jr. College, English Department, Nagasaki, Japan

References available upon request

Attn: [illegible]

The Evaluation of Using Oral Oral Sodium Phosphate, referred to FLEET, and PEG Prior to Preparation for Colonoscopy

Kaoru Matsuoka , Jyunichi Yokoyama, Satoshi Hoshiya, et al.

Preface

Usefulness of 2000 ml oral PEG is familiar in the preparation for colonoscopy, but it has the disadvantage in that patients have to take a large dosage prior to colonoscopy. For this reason, various studies have already been reported on the decreasing dosage. This treatment also requires a restricted diet and a laxative to be taken the day before treatment, which causes discomfort to patients during their daily routines. This study evaluated the usefulness of easily taken Fleet (oral sodium phosphate), commonly used in the Occidental areas, and the preference of the patients for Fleet rather than PEG. In this experiment, the patient received 90 ml of Fleet with an equal volume of water, mixed with 1000 ml of PEG once on the morning of the day of preparation for colonoscopy. The side effects were observed including the oral lavage, the subjects symptoms due to the large dosage taken and the clinical research testing.

1、Subject and Method

The study included 38 patients, 35 males and 3 females, who consented to undergo colonoscopy. The age ranged from 21 to 68, with a mean of 53.9. The participants were not on a restricted diet until the night prior to the day for colonoscopy. For the procedure the patients took 45 ml of Fleet, mixed with 45 ml of water in the morning of the preparation for colonoscopy and then received 1000 ml of PEG within one hour. There was no restriction placed on water intake. The results are shown in Table 1.

Table 1 Constituent of Fleet.

表 1 フリートの組成

フリート (100 ml 中)	
Sodium biphosphate : Na(Po₄)₂	48 g
Sodium phosphate : NaPo₄	18 g
Water	100 ml

The patients with the following symptoms were excluded from the study.

kidney disorders
myocardial infarction related symptoms such as
vascular disorder, high blood pressure, and excess of abdominal fullness,
serious colitis
electrolytic abnormality,
pregnancy, and
breast feeding

The subjects in the study answered questionnaires about potential side effects after the procedure.

A blood sample was taken prior to the preparation for colonoscopy, and the following testing was performed:

Blood analysis: Hb, RBC, Ht, WBD
Biochemistry: Na,K,Cl,Ca,IP,BUN, creatinine measured.

2. Results

The Figure 1 shows the degree of the lavage in the intestinal tract (colon) with Fleet mixed with PEG in the areas of cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and the residual feces were evaluated at four levels ranging from no residual feces, large amounts of residual feces, small amounts and none traceable. Only a small amount of residual feces was detected, almost 90% of six areas of the colon that were tested. This test result was almost similar to those of our previous evaluation of 2000 ml of PEG in the oral lavage. The feces residue tended to be observed in the colon on the right side. The side effects of mixed dosage are shown in Table 2. None of 38 patients complained of discomfort when taking the dosages.

Figure 1 The Degree of the Lavage

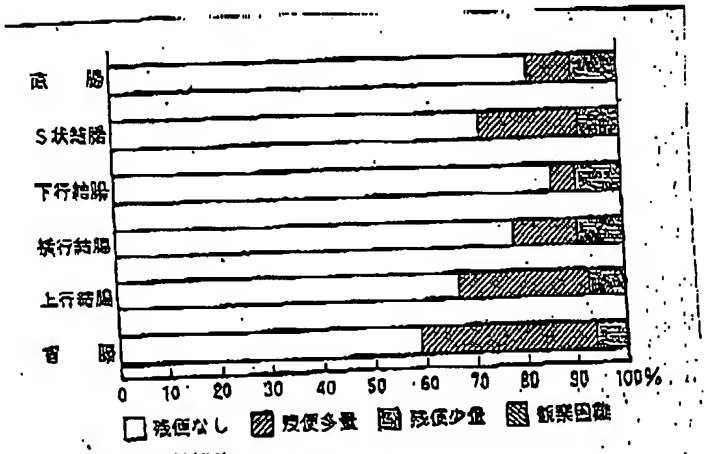


図1

Table 2 Frequency of Side Effects

表2 副作用出現率

Symptom 症状	例 (38 例中)*	出現率 (%)
nausea 嘔気	8	21.1
stomach pain 腹痛	3	7.9
abdominal fulness 腹部膨満感	3	7.9
discomfort 気分不快	1	2.6
dizziness ふらつき	1	2.6
rash (rash) 発疹	1	2.6
計	12/38	31.6%

*複数回答を含む

Twelve cases of minor side effect symptoms were noted, 31.6% and included nausea 21.1%, cramp and/or abdominal fullness, 7.9% and a minor case of discomfort, dizziness, and rash. However, serious side effects were minor and did not prevent the colonoscopy from being carried out.

The blood analysis and biochemical testing of 13 of 38 cases showed no changes In Hb, RBC, Hit, WBC, BUN, creatinine Na, K, Cl, but a significant rise observed in IP from 2.9 mg/dl to 6.1 mg/dl. However, no changes in Ca, and concurrent symptoms were not verified, as shown in Figure 2.

Figure 2 Blood Testing prior to /after the treatment

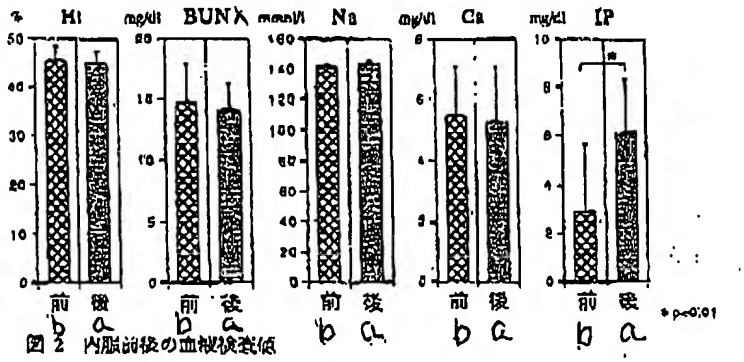


図 2 内服前後の血液検査値

前 後
before after

3. Discussion

A desirable colonoscopy procedure for cleansing the colon is:

a) It only needs to be taken as a one time preparation on the morning of the day for colonoscopy;

b) a lesser amount of solution for dosages is easily taken and comfortably by the patient;

c) a stronger lavage power exists for the patient. PEG 2000 ml preparation has an advantage of being a one time preparation on the day of colonoscopy, an isotonic solution and less side effects. However it also has the disadvantage of requiring a large dosage, which is not easy for patients to take.

Fleet has been shown useful in the Western Hemisphere and has a similar effect with that of PEG with lesser consumption of the solution in cleaning the intestinal tract. Fleet has the disadvantage in view of the fact that patients have to take treatment twice the night before and on the morning of the day of colonoscopy and these treatments were not appropriate for all patients.

Therefore, in this experiment, using Fleet mixed with PEG was evaluated for the possibility of satisfactory procedure in the preparation of a solution for colonoscopy.

Usefulness of Fleet with PEG was similar to PEG-2000ml. Disadvantages were nausea due to the salty taste, a slight elevation of IP of serum phosphate levels caused during the time of consumption, however, no serious side effects were observed. This method, therefore, was evaluated as effective/useful in the preparation for colonoscopy.

Conclusions

1) Oral lavage using PEG and Fleet was satisfactory resulting in over 90% including none of residual feces and less.
2) Patient's tolerance was increased; the patient received a small amount of PEG for a one time consumption on the day of treatment.
3) No serious side effects were observed.
4) This method was evaluated useful/effective for the preparation for colonoscopy with the restricted patients.

文 献

1) Vanner SJ *et al* : A randomized prospective trial comparing oral sodium phosphate with standard polyethylen glycol-based lavage solution (golytery) in the preparation of patient for colonoscopy. *Am J Gastroenterol* 85 : 422-427, 1990
2) Kolts BE *et al* : A comparison of the effectiveness and patient tolerance of oral sodium phosphate, castor oil, and standard electrolyte lavage for colonoscopy or sigmoidscopy preparation. *Am J Gastroenterol* 88 : 1218-1223, 1993
3) Marshall JB *et al* : Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-based lavage for colonoscopy preparation. *Gastrointest Endosc* 39 : 631-634, 1993
4) Marshall JB *et al* : Short report : Prospective, randomized trial comparing a single dose sodium phosphate regimen with PEG-electrolyte lavage for colonoscopy preparation. *Aliment Pharmacol Ther* 7 : 679-682, 1993

Fleet® Phospho-soda®

BOWEL PREPARATION INSTRUCTIONS

READ CAREFULLY. DO NOT EXCEED RECOMMENDED DOSAGE AS SERIOUS SIDE EFFECTS MAY OCCUR. (SEE PACKAGE FOR OTHER IMPORTANT WARNINGS.)

- Two days before your procedure, purchase two 1.5-oz bottles of Fleet® Phospho-soda®.
- Follow the steps listed below, or as your doctor has otherwise prescribed.
- If you are taking medication (including aspirin or aspirin-containing products), consult your doctor for additional instructions before beginning this procedure.

Importance of DRINKING LIQUIDS during the bowel preparation process:

During bowel preparation you will lose significant amounts of fluid. **THIS IS NORMAL.** It is very important that you replace this fluid to prevent dehydration. Drink large amounts of clear liquids. Drinking large amounts of clear liquids also helps ensure that your bowel will be clean for the examination.

Day Before Exam

☐ **Breakfast**
Have your regular breakfast

☐ **Morning**
Drink Clear Liquids
(See "Clear Liquids Diet List" on back)

☐ **Lunch (Before 2 PM)**
Have a Low Residue Lunch
(See "Diet Instructions" on back)

☐ **Afternoon**
Drink Clear Liquids

☐ **Dinner**
Drink Clear Liquids

☐ **7:00 PM**
Take Fleet Phospho-soda
(See "How To Take Fleet Phospho-soda" below)

☐ **Evening**
Drink 3 more glasses (8 fl. oz. each) of Clear Liquids
Check off each as you complete them.
_____#1 8 fl. oz. glass of clear liquid
_____#2 8 fl. oz. glass of clear liquid
_____#3 8 fl. oz. glass of clear liquid
Additional Clear Liquids are encouraged.

Individual response to laxatives varies. This prep may begin to work within 30 minutes to 6 hours. Remain close to a toilet as multiple bowel movements will occur.

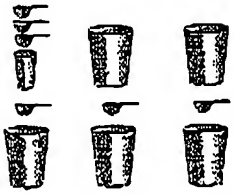
Day of Exam

☐ **6:00 AM** *(or at least 3 hours before you leave for your exam)*
Take Fleet Phospho-soda (See "How To Take Fleet Phospho-soda" below)

☐ **AM/PM**
Report for your appointment (See "Appointment Information" on back)

Low-Residue Diet

HOW TO TAKE FLEET PHOSPHO-SODA



A) Mix 1 ½ fl. oz. (3 measuring Tablespoons - NOT tableware) of Fleet Phospho-soda with at least 4 fl. oz. of cold *Clear Liquid* (ginger ale, apple juice, Sprite® or 7-Up® helps improve the taste) and drink. Then follow with 2 glasses (8 fl. oz.) of *Clear Liquid*. You may then drink all the *Clear Liquids* you like.

OR

B) Mix ½ fl. oz. (1 measuring Tablespoon – NOT tableware) of Fleet Phospho-soda into a glass (8 fl. oz.) of cold *Clear Liquid* (ginger ale, apple juice, Sprite® or 7-Up® helps improve the taste) and drink. Repeat two more times within the next 20 minutes. You may then drink all the *Clear Liquids* you like.

Fleet pharmaceuticals

EXHIBIT
tabbies
F